example, at page 6, lines 21-27. Applicants have added claims 26 and 27, which are supported in the specification, for example, at page 11, lines 3-12.

II. Rejection under 35 USC §112, first paragraph

The examiner has rejected claims 24 and 25 for the lack of the written description alleging that the limitation, "co-localization" is not supported by the original specification. As explained above, applicant has obviated the rejection by replacing the reference to "the co-localization" with the recitation of "co-expression." This amendment, however, does not constitute acquiescence to the propriety of the examiner's position, and is simply made to advance the case towards allowance. Because this amendment renders the rejection moot, applicant respectfully requests withdrawal of the rejection.

III. Rejections under 35 USC §103(a)

A. Summary of the Rejections

The examiner has rejected claims 20-25 as allegedly obvious over Toi *et al.* ("Toi"), Battegay, Rockwell *et al.* ("Rockwell"), or Janjic *et al.* ("Janjic"), in view of Hanna, Jr. *et al.* ("Hanna") or De Jager *et al.* ("De Jager"). The examiner has also rejected claims 20-25 as allegedly obvious over Boocock *et al.* ("Boocock"), Warren *et al.* ("Warren"), or Halva *et al.* ("Halva") in view of Hanna or De Jager. Finally, the examiner has rejected claims 20-25 as obvious over Toi, Battegay, Rockwell, Janjic, Boocock, Warren or Halva in view of Hanna or De Jagar and further in view of Kendal et al. ("Kendal").

The examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art to use the known methods and materials of tumor and metastasis detection using localization including the *in vivo* detection techniques such as CAT-scan exemplified in Hanna or De Jager, with the antibodies or receptor proteins to the known metastatic indicator VEGF and its receptors taught in Toi, Battegay, Rockwell, Janjic, Boocock, Warren and Halva, and that one would have been motivated to do so because VEGF and its receptors are useful for detecting metastasis, as taught by Toi, Battegay, Rockwell, Janjic, Boocock, Warren and Halva.

With respect the use of VEGF receptor conjugated protein as claimed in claim 22, the examiner asserts that it would have been *prima facie* obvious to one of ordinary skill inn the art to combine the *in vivo* methods of detecting metastasis using VEGF taught by Toi, Battegay, Rockwell, Janjic, Boocock, Warren or Halva, and Hanna or De Jager by using a VEGF receptor fusion protein or a VEGF receptor conjugated protein, as taught by Kendall, and that one would have been motivated to do so because VEGF receptor proteins bind tightly to VEGF *in vivo* as taught by Kendall, and thus would be effective for detecting VEGF.

Applicant respectfully traverses all the obviousness rejections.

B. Applicant's Arguments

To establish a *prima facie* case of obviousness, the examiner bears the initial burden by providing factual evidence that meets the following three basic criteria.

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, a prior art reference (or references) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). If the examiner does not produce a *prima facie* case, applicant is under no obligation to submit evidence of nonobviousness.

Here, the examiner has not set forth a *prima facie* case of obviousness. The examiner has offered ten (10) separate references, among which seven (7) primary references have been cited to support the examiner's position that VEGF was a known metastatic indicator at the time of applicant's invention. As explained in more detail below, however, none of these primary references provides teachings or suggestions that would have led one of ordinary skill in the art to recognize that VEGF can be a single and independent indicator of metastasis, and thus to use VEGF to detect metastasis in a human. None of the primary references teaches or suggests detecting overexpression of VEGF at a site distal from the primary tumor for detecting metastasis

in a human. Furthermore, the primary references do not teach or suggest an *in vivo* detection of VEGF using a detectably labeled ligand that specifically recognize VEGF to detect metastasis.

At most, the disclosures of these references are limited to the detection of (over)expression of VEGF in tumors that are already identified for their tumor status as either primary tumors or metastases. Thus, it rather evidences that mere detection of (over)expression of VEGF in patients cannot determine the status of tumors, either metastases or primary tumors, which is not previously identified, let alone metastasis of primary tumors.

As described in the specification, it has been speculated that bFGF and VEGF act synergistically, and that highest levels of bFGF were found in patients with metastatic disease. Furthermore, similar to VEGF, these high levels of bFGF in tumor cells were understood to correlate with MVD in the tumor specimens. See page 4, lines 9-22. However, notwithstanding all these suggestions, the inventors of the present invention found out that VEGF, not FGF, can be independently used as a marker of a metastasis.

However, none of the primary references provides teachings or suggestions that would have led one of ordinary skill in the art to recognize VEGF as an independent indicator of metastasis, which enables the detection of metastasis in patients whose tumor status has not been identified.

The secondary references do not cure the deficiency of the primary references. The secondary references only disclose the use of an antibody that recognizes tumor-associated antigens to localize metastases. None of the secondary references teaches the use of an antibody of VEGF, let alone the use of such an antibody for detecting metastasis. Therefore, there is neither suggestion nor motivation in the references relied upon by the examiner to combine the primary and secondary references to provide a method of detecting metastasis based on the overexpression of VEGF at a site distal from a primary tumor, as instantly claimed.

Thus, applicant respectfully submits that the examiner has not met the burden of establishing a *prima facie* case of obviousness regarding the presently pending claims. Accordingly, the rejection should be withdrawn.

Applicant discusses each cited reference below in more detail.

Toi

Toi relates to the study of the significance of the microvessel density (MVD) as an indicator and of the association between the increase in MVD and the expression of VEGF.

While Toi teaches that MVD is a significant and independent indicator as potent as the number of metastatic nodes, nowhere does Toi teach or suggest that VEGF can be independently used to detect metastasis without the corroborative information on MVD. Indeed, Toi does not mention at all the detection of metastasis by detecting the expression of VEGF.

Rather, Toi shows contradictory results between univariate and multivariate analysis in a test conducted to investigate a prognostic value for the relapse-free survival (RFS). More specifically, Toi reports that "multivariate analysis showed no independent statistical significance of VEGF." See page 202, left column, last line to right column, line 2.

As a result, despite the speculation of a close association between VEGF expression and the increase in MVD, Toi's teaching is limited to indicate that "VEGF plays important roles in the neovascularization of primary breast cancer," without recognizing VEGF as an independent prognostic indicator of RFS. Indeed, only MVD and the number of metastatic nodes are referred to as a significant prognostic indicator for RFS among variables tested that include VEGF.

Thus, contrary to the examiner's understanding, one of ordinary skill in the art would not infer from the teachings of Toi regarding the association between MVD and VEGF that VEGF has a prognostic value for metastasis, and thus can be used to detect metastasis without MVD. Rather, Toi teaches away of using VEGF as a single and independent indicator of metastasis by presenting contradictory results of using VEGF as an indicator of RFS.

Furthermore, Toi provides no hint that the detection of VEGF at a site distal from a primary tumor has a significant prognostic value for metastasis. Indeed, Toi observes

the VEGF expression in a primary tumor only. More specifically, Toi describes that "[a]proximately 50% of primary tumors were determined as VEGF positive by this antibody." (See page 202, left column, lines 9-11 from the bottom.) Thus, nothing in Toi teaches or suggests that detection of VEGF at a site distal from a primary tumor can be used to detect metastasis.

Battegay

Similarly, Battegay does not teach or suggest detecting the VEGF expression for detecting metastasis, let alone detecting the VEGF expression at a site distal from a primary tumor.

The law is quite clear that "obvious to try" is not the standard for determining obviousness under §103. "A general incentive does not make obvious a particular results, nor does the existence of techniques by which those effects can be carried out." *In re* Deuel, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

Battegay discloses that "[e]xpression of vascular endothelial growth factor (VEGF) is associated with or induced by hypoxia in ocular angiogenesis...and various tumors, tumor cell lines, fibroblasts...and smooth muscle cells." (See page 334, left column, second paragraph.) Battegay further describes that "tumor growth and the concurrent switch to an angiogenic tumor phenotype is associated with increased secretion of angiogenic molecules such as FGF, VEGF, and others." See page 334, right column, third paragraph.

However, there are no teachings or suggestions in Battegay that VEGF is a significant and independent indicator of metastasis, and thus its detection can be used for detecting metastasis. At best, Battegay might be viewed as providing a general incentive to examine whether VEGF, or other factors disclosed in Battegay, has a direct role in the development of metastasis, and thus can be used to detect metastasis. However, nothing in Battegay leads one of ordinary skill in the art to recognize and select VEGF to be used for the detection of metastasis. Therefore, the examiner applies an improper "obvious to try" rationale in support of the obviousness rejection here.

In any event, nowhere does Battegay teach or suggest that abnormal presence of VEGF at a site distal to a primary tumor can be used to detect metastasis.

Rockwell

A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Also, a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 552 (Fed. Cir. 1994).

Disclosure of Rockwell clearly evidences that it provides suggestion of abnormal presence of VEGF in proximity to a primary tumor rather than distal to the primary tumor by failing to recognize the abnormal presence of VEGF at a site distal from a primary tumor. Specifically, as also noted by the examiner at page 4, line 2 from the bottom of the Office Action, Rockwell teaches that "up regulation of VEGF and receptor is in proximity to the tumor."

Indeed, there are no teachings or suggestions in Rockwell that guide a skilled artisan to select VEGF to detect metastasis as in the claimed invention. Therefore, one of ordinary skill in the art would not infer from Rockwell that detection of VEGF expression at a site distal from a primary tumor can be used for this purpose.

Janjic

Janjic discloses VEGF as one of the major angiogenesis inducers *in vivo*, as also noted by the Examiner. Janjic, however, does not teach or suggest the abnormal presence of VEGF that is detected at a site distal from a primary tumor, can be used to detect metastasis.

Moreover, a closer reading of Janjic reveals that its disclosure is limited to the VEGF expression in tumor cells facing necrotic areas. See column 2, third paragraph. That is, Janjic only observes the expression of VEGF in necrotic sites adjacent to a primary tumor, but fails to teach the VEGF presence at a site distal from the primary. Thus, Janjic evidences no motivation for one of ordinary skill in the art to use the

expression of VEGF that is detected at a site distal to a primary tumor as an indicator of metastasis, as in the claimed method.

Boocock

Detecting VEGF as well as its receptors, flt and KDR, which are expressed in tumor cells and metastatic ovarian carcinoma, Boocock suggests that VEGF may stimulate angiogenesis and promote tumor progression acting through its receptors. However, nowhere does Boocock teach or suggest that VEGF can be used to detect metastasis.

The disclosure of Boocock is limited to the detection of VEGF in tumors whose status is already identified as either primary tumors or metastases. Furthermore, Boocock only shows detection of VEGF in cultured tumor cells, but does not disclose an *in vivo* detection of VEGF. Therefore, contrary to the examiner's assertion, Boocock fails to teach or suggest VEGF as a detector of metastasis, and thus simply does not discloses a method of detecting metastasis as instantly claimed.

Warren

Warren does not cure the deficiency of Boocock. Similar to Boocock, what Warren discloses is the detection of VEGF in tumors whose status is already known as metastases, but not the detection of metastasis by using VEGF as an indicator. Although Warren reports the suppression of liver metastases using anti-VEGF monoclonal antibody, the human colon carcinoma line (HM7 cells) inoculated in a liver was already known to have a high potential for spontaneous liver metastasis. Therefore, such test results still have not substantiate the fact that the abnormal expression of VEGF at a site distal from a primary tumor can be used to detect metastasis.

Halva

Halva does not cure deficiencies of other primary references. That is, *Halva* detected the expression of VEGF, together with its receptors, Tie, KDR and Flt1, in the majority of low-grade tumors, malignant glioma, and melanoma metastases. However,

Halva evaluates this finding as a mere suggestion that VEGF has a role as an *in vivo* tumor angiogenesis factor.

As explained above, however, a mere finding of the role of VEGF as an angiogenesis factor would not have led one of ordinary skill in the art to recognize VEGF as an independent indicator of metastasis and to use the expression of VEGF to detect metastasis.

Furthermore, in contrast to the claimed invention, Halva observed the VEGF expression immediately adjacent to necrotic foci and suggests that the growth factor may be induced in the tumors under conditions of hypoxia. See page 375, right column, lines 1 to 4. However, as explained above, the claimed method detects abnormal expression of VEGF at a site distal from a primary tumor. Thus, *Halva* evidences no motivation for one of ordinary skill in the art to use VEGF as an indicator of metastasis, which is detectable at a site distal to a primary tumor, as in the claimed method.

* * *

In sum, none of the primary references teaches or suggests that VEGF can qualify as an independent indicator of metastasis. Indeed, given the limited teachings of the cited references, one of ordinary skill in the art would not have chosen VEGF from other known angiogenic factors to use it to detect metastasis by detecting its abnormal expression at a site distal from primary tumors.

None of the secondary references cures this deficiency. As indicated by the examiner, the secondary references, Hanna and De Jager only disclose the *in vivo* detection of cancer including metastases using antibodies or receptors to localize a known cancer antigen. That is, these references are only concerned with general detection of cancer antigen other than VEGF. While *Kendal* teaches the use of endogenous soluble receptor to inhibit VEGF, *Kendal* does not teach the use of endogenous soluble receptor to detect metastasis. There is no disclosure in the secondary references that implicates or suggests the use of a labeled ligand that recognizes VEGF for the detection of metastasis.

Therefore, there is no suggestion or motivation in the combination of the cited references to combine the primary and secondary references to use a labeled ligand that recognize VEGF including a VEGF-antibody to detect metastasis.

In conclusion, given the specific elements recited in the claims as amended, and the failure of the cited art to recognize the critical importance of detecting the abnormal presence of VEGF at a site distal from a primary tumor for diagnosing a metastatic potential of the primary tumor, the cited references, alone or in combination, do not render obvious the claimed invention. Accordingly, applicant respectfully requests withdrawal of all the obviousness rejections.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date September 20, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Marked up rewritten claims:

20. (Twice Amended) A method of [diagnosing] detecting metastasis at a site distal from a primary tumor in a human comprising:

a) administering to the human a detectably labeled ligand which specifically recognizes VEGF [to the human]; and

b) detecting the labeled ligand in the human, wherein abnormal [localization] presence of the labeled ligand indicates overexpression of VEGF at a site distal from the primary tumor and further indicates the presence of metastasis in the human.

21. (Amended) The method of claim 20 wherein the [presence] overexpression of VEGF is determined using an anti-VEGF antibody.

22. (Amended) The method of claim 20 wherein the [presence] overexpression of VEGF is determined using a VEGF receptor fusion protein or VEGF receptor conjugated protein.

23. (Amended) The method of claim 20 wherein the [localization] presence of the ligand is detected using a method entailing X-ray, CAT-scan or MRI.

24. (Amended) The method of claim 20, further comprising detecting [the co-localization] co-expression with VEGF of tyrosine kinase receptors involved in angiogenesis.